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Brainnetome and related projects

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The brain is organized as a hierarchy of complex networks on different temporal and spatial scales. The complex connectivities within the brain are presented in the anatomical architecture as well as dynamic activity. There have long been efforts to make a connection map of the brain [1], and this has now been achieved with the establishment of the connectome [2]. The connectome framework is of central significance for understanding how the brain works at a detailed level [3], however, the connectome can only provide a structural description of the brain [2]. It is essential to understand the brain through integrating multi-level network features obtained using various functional and anatomical brain imaging technologies on different scales, from the finest (ultramicrotomy, staining techniques) to the most macroscopic (functional MRI, diffusion MRI, electroencephalography). The brainnetome (brain-net-ome) was proposed to meet this need [4]. It is a new "-ome" in which the brain network is the basic research unit by which the hierarchy in the brain can be studied. The two components of the brainnetome, namely nodes and their connections, can be defined at different scales with different techniques. The brainnetome includes at least the following five research themes: (i) identification of brain networks, (ii) dynamics and characteristics of brain networks, (iii) network manifestations of functions and malfunctions of the brain, (iv) genetic basis of brain networks, and (v) simulation and modeling of the brainnetome [4]. The concept of the brainnetome has received impetus from a number of programs and projects in China. In 2010, a project supported by the National Basic Research Program of China (973 Program), called the Brainnetome Project, was launched in China and focused on the macroscale parts of the brainnetome. A number of projects related to the brainnetome were launched recently, and several more are due to be launched, in China, Europe and the USA.

The brainnetome is an open framework and the new projects launched in China, Europe and the USA fit into this framework. The Brain Project has been one of the strategic research priorities in China for more than 20 years. The Ministry of Science and Technology of China (MOST) is one of the major funding sources for brain research in China. The first big project on the brain was launched in 1999, which was supported by the National Basic Research Program of China run by MOST. From here on in, we call this type of project a "973 project". Since 1999, more than 50 such projects related to the brain and its disorders have been supported in China. In 2010, a 973 project called the Brainnetome Project was launched, but it focused solely on the macroscale parts of the brainnetome, as another 973 project on microscale neural circuits was approved at the time. The microscale project has since been upgraded, and now focuses on the neural basis of human intelligence. It includes

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the formation, function and plasticity of neural circuits, which is one part of the brainnetome on a microscale.

The National Natural Science Foundation of China (NSFC) is another important funding source for brain research in China. In 2011, the Grand Research Plan for Neural Circuits of Emotion and Memory was launched by NSFC. The Chinese Government invested 200 million RMB in this program for eight years. There is a possibility for further funding (up to 50 million RMB) after a mid-term review. This program focuses on how emotion and memory and their disorders are manifested in brain networks on different scales and what new techniques can meet this need. In the first three years, it supported a group of projects on specific research topics. In the future, it will support a small number of bigger projects, which are aimed at making major breakthroughs in the brainnetome field.

The Chinese Academy of Sciences (CAS) also plays an essential role in funding brain research. In 2012, CAS approved one of the Strategic Priority Research Programs, called the Functional Connectome Project, for funding. Three hundred million RMB was invested in this program for five years. There is a possibility to renew funding from CAS for another five or 10 years, or possibly even longer. The goals of this program are to dissect the functional atlas of brain networks for perception, memory, emotion, and their disorders as well as to develop advanced technologies to achieve these goals. It also aims to encourage collaboration among interdisciplinary researchers through continuous support for up to 25 top laboratories devoted to brain network studies in China. Though the NSFC and CAS programs seem to be devoted to network manifestations of function and malfunction of the brain, they will involve all five aspects of the brainnetome. The ultimate goals of these programs are to improve our understanding of the brain and to find new biomarkers for early diagnosis, prognosis, and drug-effect evaluation of psychiatric and neurological diseases, which is a key goal of the brainnetome [5].

In early 2013, the European Union launched the Human Brain Project, which is closely related to simulation and modeling of the brainnetome. This is a very ambitious project. It has a clear goal, but we cannot find a detailed research plan in its report. The big challenge is how to organize and implement it when so many institutions are involved in such a super-project. The USA also launched its BRAIN Project in April of 2013. After five months of discussion, nine priorities were selected and these priorities will be used for funding guidance in 2014. In fact, many research themes of the BRAIN Project in the USA have been included in various brain projects in China, especially those projects related to the brainnetome. If we are to compare the HBP in Europe and BRAIN Project in the USA to the current projects related to the brainnetome in China, it appears that the Chinese projects are focused on the human brain and clinical outcomes, and have a more practical research plan. Since March of 2013, a number of meetings have been organized by the Chinese Government to discuss what kind of China Brain Project should be launched in the future.

To encourage collaboration in the field of brainnetome research, a number of international organizations and laboratories have been established or will be established in the near future. The first laboratory to be established in this field was the Neuroimaging and Brainnetome Laboratory at the Queensland Brain Institute (QBI), The University of Queensland (UQ), Australia in 2011. Based on this collaboration, a new joint laboratory between CAS and UQ was launched in March of 2013, which is named the Joint Sino-Australian Laboratory of Brainnetome. It has bases both at CAS Institute of Automation (CASIA) in Beijing and at QBI in Brisbane. The Joint Laboratory aims to map brain organization using advanced imaging techniques and to develop a greater understanding of how brain networks function in both diseased and normal states. The first research projects undertaken by the joint laboratory include elucidating the brainnetome of genetically modified mice for neuropsychiatric diseases, and brainnetome-wide association studies of schizophrenia, depression and Alzheimer's disease. Future projects will build on complementary strengths in cognitive neuroscience to tackle other areas of significance such as learning and education. As the Senior Professorial Fellow appointed to this project, I am responsible for overseeing the establishment and development of the joint research laboratory. On the UQ side, I have three Ph.D. candidates and one postdoctoral researcher, and a number of the QBI faculty are affiliated with this joint laboratory. On the CASIA side, nine faculty members and 10 Ph.D. students are working in this joint laboratory. Since QBI and CASIA share common interests in neuroimaging and the brainnetome, and have complementary expertise and facilities in the field, such collaborative research and scientific exchange through this joint laboratory will be mutually beneficial and will provide new insights into brain organization and its function, which will be applied into developing novel therapeutics to treat the avalanche of brain-based diseases affecting the two countries as well as the rest of the world.

In 2012, a new department, the Brainnetome Center, was approved by CASIA. The research topics of this center cover all aspects of the brainnetome. Moreover, the Chinese Society of the Brainnetome, a new branch of the Chinese Society for Anatomical Sciences, was launched in early of 2013. Based on the Functional Connectome Project, one of the Strategic Priority Research Program, CAS, is planning to establish a cross-institute center, the Center of Excellence in Brain. It will be based in the Institute of Neuroscience of

CAS in Shanghai. In its first stage, it will include top neuroscientists from six institutes of CAS, which are distributed in Shanghai, Beijing, Wuhan, Kunming, and Shenzhen. It will support up to 50 world-class principal investigators. It is envisioned that it will be a key component of the China Brain Project in the future.

Great progress has been made in the brainnetome and many projects have been launched in this field, however, a large number of challenges remain. The first challenge is to construct the multiscale brain atlas. Brain atlases are basic tools to study the immensely complex organ and further understand its inner workings. With a history of more than a century, the 'Brodmann areas' are still used most often as one of the possible parcellations of the human cortex. Previous studies have clearly shown the limitations of the Brodmann areas and the importance of defining cortical areas by multiple criteria. For the last two decades, the human brain mapping approaches at various spatial and temporal scales have undergone an unprecedented development.

One of the next generation brain atlases is the "Brainnetome Atlas", which will provide finer subdivision of the brain regions and their connectivity patterns. Novel methodologies and computerized brain mapping techniques will be developed to study the structure, function, and spatio-temporal changes in the human brain as well as the brains of non-human primates. The brainnetome atlas will be an *in vivo* map, with more fine-grained functional brain subregions and detailed anatomical and functional connection patterns for each area, which could help researchers to more accurately describe the locations of the activation or connectivity in the brain. At this stage, the brainnetome atlas will facilitate investigations of structure-function relationships, comparative neuroanatomical studies, and promises new biomarkers for diagnosis and clinical studies. In the next step of the construction of the brainnetome atlas, it will go local instead of global and dynamic instead of static, which will be along with the other brain mapping information, such as genetic expression patterns, connectivity patterns and the spatio-temporal dynamic changes during normal development and the aging process, or in different disease states. The optimized framework to combine the more fine-grained *in vivo* parcellation brain atlas with maps of gene expression and connectivity will provide entirely novel insight into our understanding of the brain. By better understanding the genetic control and manipulation of brain parcellation and effects on brain connectivity patterns, we will also have a profound impact on the field of human brain mapping research. Furthermore, in order to complete such brain maps across different scales, the collaboration between multiple brain research institutes from different fields will be necessary for the next generation brain atlas. For example, in future it will be necessary to develop micro-imaging methods to map the nervous system at the microscale.

The second challenge in the brainnetome is the convergence of the brainnetome with other "-omes", which will be important for understanding the brain and its disorders. To encourage the integration of the brainnetome with the genome, especially in psychiatric research [6], the "The Symposium on Brainnetome Meets Genome (SBMG)" was established. It was inaugurated by QBI and CASIA in 2012, with the first event being held in Brisbane that same year and the second being held in Beijing in 2013. At this symposium, international scientists gather to explore the latest research and challenges relating to brain networks and how genes modulate brain networks. Although such efforts have been made, great challenges remain for the integration of the brainnetome and other "-omes" at different levels, especially those in which analytical, statistical, and visualization techniques are used (Figure 1). Many topics should be tackled through future interdisciplinary efforts, for example, between biology, medicine, informatics, mathematics and engineering.

The third challenge in the brainnetome is big data. The developments of neuroscience technologies have revolutionized our ability to obtain full anatomical pictures of whole animal brains, to trace the circuits involved in specific functions, and to non-invasively map the human brain *in vivo*, including manifesting the shape and size of brain areas, imaging the fibers linking different brain areas, and elucidating the brain networks and pathways responsible for specific functions. The deluge of these complex and heterogeneous data pose significant challenges for the informatics community. Some novel techniques should be developed to store, manage and analyze these data. More storage spaces and faster processing workstations/clusters are surely required. Developing clever algorithms that help to efficiently extract knowledge from these data are one of the key challenges.

Finally, it is also a big challenge to push private organizations and companies to support the brain research, especially in China. The diversified investment approach is one of the important characteristics of the scientific system in western countries. Nowadays, non-profit private organizations and foundations play important roles in the promotion and support of scientific research concerning the brain. The BRAIN Initiative, for example, is supported not only by the US Federal Government, including the National Institutes of Health, the National Science Foundation and the Defense Advanced Research Projects Agency, but also by several private foundations and research institutes, including the Allen Institute for Brain Science, the Howard Hughes Medical Institute, the Kavli Foundation, and the Salk Institute

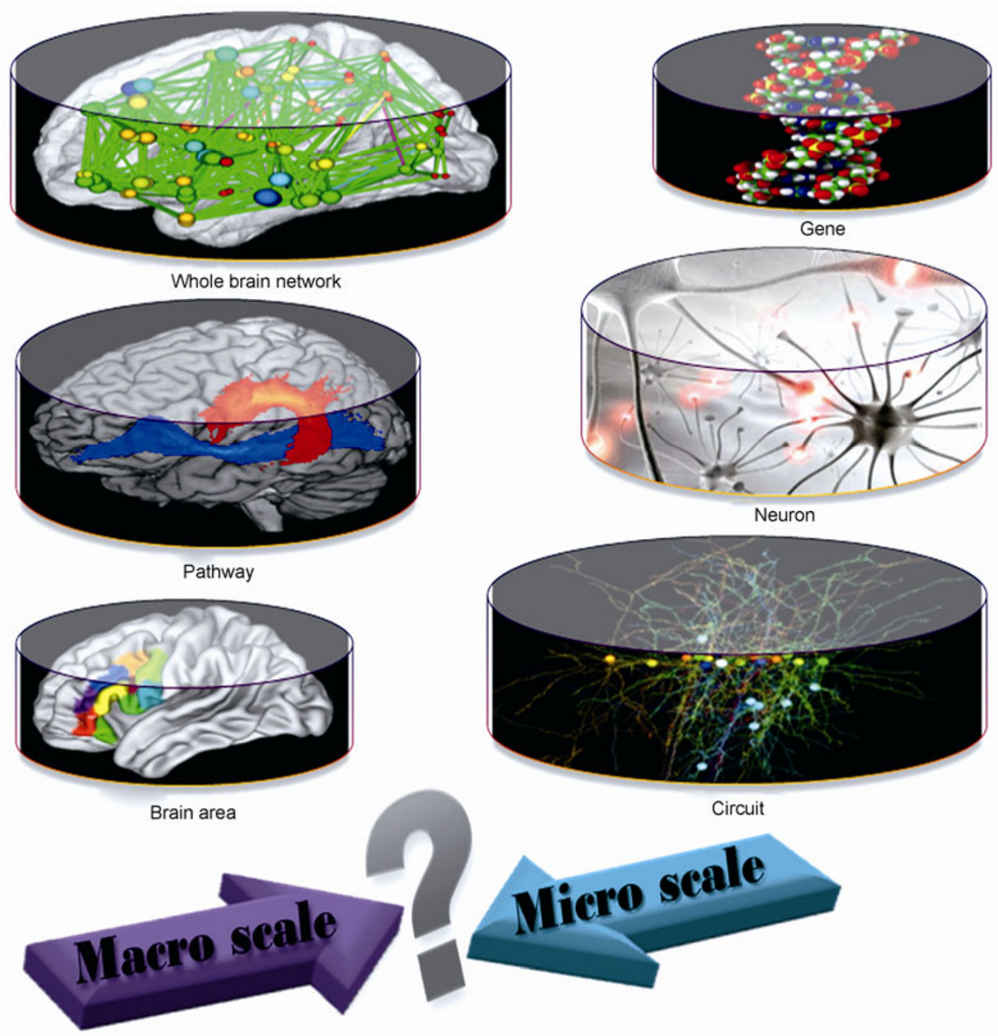

Figure 1 Challenges for bridging the gap between micro- and macroscale brain network studies. On each scale, from gene, neuron and neuronal circuit, to brain area, pathway, and the whole brain, many advances have been made. The challenges are to develop new techniques to integrate the studies of the brainnetome from two different directions at the macro- and microscales (with permission from Elsevier).

for Biological Studies. Though the private foundation funding for scientific research is limited, the flexibility and openness of this funding can give researchers an advantage that government funding does not allow. In many cases, private funding can provide financial support that complements existing government funding. In recent years, the foreign private organizations and foundations have begun to focus on investment of the brain science research in China. For example, since early 2011, the International Data Group (IDG) has sealed donation agreements with Tsinghua University, Peking University and Beijing Normal University (BNU) to establish IDG/McGovern Institutes for Brain Research.

With the development of the social economy in China, especially the accumulation of private wealth and the reformation of the tax policy, it is both timely and possible to promote and encourage the development of private foundations. There is no doubt about the dominant role of the government in promoting scientific and technological progress, as it is able to act in a very systematic way and at such a large scale that private foundations can only ever hope to match. Therefore, philanthropists, private institutions, and government need work together to promote the progress of brain research in the future. For the future China Brain Project, the state should adopt various forms to enrich brain research investment entities and establish a diversified investment system.

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